We showed previously that ambrisentan, a selective endothelin type A receptor antagonist, and tadalafil, a PDE5 inhibitor, act synergistically to relax endothelin-constricted pulmonary arteries (Liang et al. Hypertension 2012; 59: 705-11). To confirm these findings in an in-vivo model of PAH, we investigated the effect of ambrisentan and tadalafil in combination on hypoxia-induced PAH in rats. Upon exposure to hypoxia (10% $O_2$), male SD rats were dosed with vehicle, ambrisentan (1 mg/kg, q.d.), tadalafil (10 mg/kg, q.d.) or the combination via oral gavage for 3 weeks. Three weeks of exposure of rats to hypoxia increased mean pulmonary arterial pressure (mPAP) from 10.8 &plusmn0.7 mmHg (normoxic, mean &plusmn SEM, n = 8) to 23.9 &plusmn1.3 mmHg (hypoxic, n = 12, p < 0.01 vs normoxic). Teatments with ambrisentan, tadalafil and the combination reduced mPAP to 20.1 &plusmn0.8 mmHg (n = 12, p < 0.05 vs hypoxic), 20.8 &plusmn1.2 mmHg (n = 11, p < 0.05 vs hypoxic) and 15.9 &plusmn1.0 mmHg (n = 12, p < 0.01 vs hypoxic), respectively. Chronic exposure of rats to hypoxia also increased the ratio of right ventricle weight/ left ventricle weight (RV/LV) from 0.326 &plusmn0.013 (normoxic, n = 8) to 0.602 &plusmn0.019 (hypoxic, n = 12, p < 0.01 vs normoxic). The ratios of RV/LV from hypoxic rats dosed with ambrisentan, tadalafil and the combination were decreased to 0.527 &plusmn0.014 (n = 12, p < 0.05 vs hypoxic), 0.531 &plusmn0.016 (n = 11, p < 0.05 vs hypoxic) and 0.430 &plusmn 0.017 (p < 0.01 vs hypoxic). Consistent with the in-vitro pulmonary artery data, the combination of ambrisentan and tadalafil caused a greater effect than each drug alone or the calculated sum of the individual effects of each drug, suggesting that ambrisentan and tadalafil synergistically attenuate hypoxia-induced PAH in rats.

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## Real world experience in the DETECT study for pulmonary artery hypertension associated with systemic sclerosis

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Objectives: The currently ongoing DETECT study, a two-stage, prospective, observational, cohort study in systemic scleroderma (SSc) patients to evaluate screening tests and the incidence of pulmonary arterial hypertension (PAH) and pulmonary hypertension, is attempting to refine the screening process in pulmonary artery hypertension associated with SSc. We adopted the same multiple screening tests forced vital capacity [% predicted]/DLCO [% predicted]; current/past telangiectasias; anti-centromere antibody; N-terminal pro-brain natriuretic peptide; uric acid; right axis deviation on electrocardiography) in patients with SSc in our hospital to evaluate its Method: Date from 21 SSC patients, who had undergone right heart catheterization from 2009 to 2012 in our hospital, were retrospectively analyzed. We compared the result of DETECT screening system to mean pulmonary artery pressure assessed by right heart catheterization. Results: Seventeen SSc patients (80.9%) were categorized as candidates to referral to right heart catheterization in this study. Overall sensitivity was 100% and specificity was 25%. Conclusion: According to the 2012 American College of Rheumatology Annual Meeting, DETECT algorithm was announced that its sensitivity was 96% and specificity was 48%. Therefore, our results indicated that DETECT algorithm had the possibility to overestimate the risk of PAH in SSc patients.

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## Reduced circulating endothelin-1 Level in uncorrected ASD patients with severe pulmonary hypertension

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There is increased risk of pulmonary hypertension (PH) in patients with Atrial Septal Defect (ASD), although the factors associated have not been clearly defined. Endothelin-1 (ET-1), a potent vasoconstrictor derived mainly from pulmonary endothelium, has been reported to be elevated in PH associated with congenital heart defect (CHD). However, studies about CHD-related PH included only a small number of ASD-patients and most of them were performed in children. In this study, we aim to measure the circulating ET-1 level in adult patients with uncorrected ASD complicated by severe pulmonary hypertension. Fifty-two newly diagnosed ASD patients were participating in this study, aged 20–79 years old. Measurements of RVSP, characteristics of ASD, remodeling RV were performed using TTE and TEE. The hemodynamic measurement by echo showed significant correlation with right heart catheterization ($r = 0.8; p < 0.0001$). Peripheral blood was withdrawn from brachialis vein and circulating ET-1 was measured using ELISA. Severe PH were defined as RVSP > 60 mmHg. The severe PH group (n = 25) was confirmed by larger RA diameter, larger RV diameter, reduced RV systolic function, and higher tricuspid valve gradient as compared to non-severe PH group (n = 27) ($47.6 \pm 1.47$ vs. $41.2 \pm 1.24$ mm; $p < 0.01$; $48.6 \pm 1.16$ vs. $41.2 \pm 1.29$ mm; $p < 0.001$; $21.9 \pm 1.01$ vs. $25.9 \pm 1.45$ mm; $p < 0.0001$; $92 \pm 5.5$ vs. $33.7 \pm 1.88$ mmHg; $p < 0.0001$; respectively). There were no differences of age, diameter of the defect, and pulmonary flow ratio in the severe PH group. Interestingly, the circulating plasma ET-1 level was significantly lower in the severe group ($6.3 \pm 0.48$ vs. $4.7 \pm 0.32$ pg/dl; $p < 0.01$). In conclusion, we reported lower circulating plasma ET-1 in ASD patients with severe PH. Further study should be performed to elucidate the ET-1 level in pulmonary circulation in this disease.

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## Current state of medicine usage and the predictor of mortality in pulmonary arterial hypertension in Japan

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Background: Endothelin receptor antagonist (ERA) is recommended for treatment of pulmonary arterial hypertension (PAH). However, recommendation is based on reports of monotherapy. Method: We examined consecutive 112 patients diagnosed with Group 1 and 1' PAHwho visited 14 affiliated hospitals from July 2006 to January 2013. The difference in mortality between monotherapy group and combination therapy group (ERA and other PAH drugs) was compared. Results: There were 41 idiopathic, 43 collagen tissue disease, 24 congenial heart disease and 4 other types of PAH. Mean age was 52.2 years old, female 66.1%, WHO Functional Class1 5.6%, 2 31.5%, 3 53.9%, 4 9.0%, BNP 128 (49.3–406.5) pg/mL, cardiac index $3.4 \pm 1.6$ (L/kg/m2), mean pulmonary arterial pressure